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EP 99/10176

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

98204347.3

PRIORITY DOCUMENT
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Im Auftrag

For the President of the European Patent Office

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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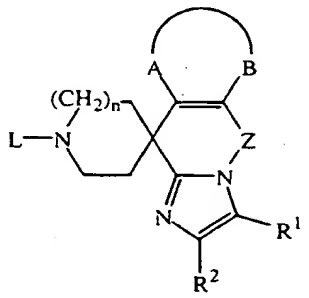
ANTIHISTAMINIC SPIRO COMPOUNDS

The present invention is concerned with spiro compounds having antihistaminic activity. It further relates to their use as a medicine, their preparation as well as compositions comprising them.

WO 97/24356, published on 10 July 1997, discloses 4-(imidazo-azepine) piperidine spiro derivatives as intermediates in the preparation of 1-(1,2-disubstituted piperidinyl)-4-(imidazo-azepine) piperidine spiro derivatives having tachykinin antagonistic activity.

Surprisingly, the 4-(imidazo-azepine) piperidine spiro derivatives of the present invention show an interesting antihistaminic activity profile.

The present invention concerns compounds of formula (I) for use as a medicine, characterized in that the compounds of formula (I) are defined as



(I)

their prodrugs, *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms wherein

R^1 is hydrogen, C_{1-6}alkyl, halo, formyl, carboxyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl-carbonyl, $N(R^3R^4)C(=O)$-, $N(R^3R^4)C(=O)N(R^5)$-, ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, $N(R^3R^4)C(=O)$-, C_{1-6}alkyl$C(=O)N(R^5)$-, C_{1-6}alkyl$S(=O)_2N(R^5)$- or $N(R^3R^4)C(=O)N(R^5)$-;

wherein each R^3 and each R^4 independently are hydrogen or C_{1-4}alkyl;

R^5 is hydrogen or hydroxy;

R^2 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, $N(R^3R^4)C(=O)$-, aryl or halo; or

n is 1 or 2;

-A-B- represents a bivalent radical of formula

-Y-CH=CH- (a-1);

-CH=CH-Y- (a-2); or

-CH=CH-CH=CH- (a-3);

wherein each hydrogen atom in the radicals (a-1) to (a-3) may independently be replaced by R^6 wherein R^6 is selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, formyl, carboxyl and hydroxycarbonylC_{1-6}alkyl;

each Y independently is a bivalent radical of formula -O-, -S- or -NR^7-;

wherein R^7 is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

Z is is a bivalent radical of formula

$-(CH_2)_p-$	(b-1),
-CH=CH-	(b-2),
$-CH_2-CHOH-$	(b-3),
$-CH_2-O-$	(b-4),
$-CH_2-C(=O)-$	(b-5), or
$-CH_2-C(=NOH)-$	(b-6),

provided that the bivalent radicals (b-3), (b-4), (b-5) and (b-6) are connected to the nitrogen of the imidazole ring via their $-CH_2-$ moiety;

wherein p is 1, 2, 3 or 4;

L is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl or C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, polyhaloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or polyhaloC_{1-4}alkyloxy.

The compounds of formula (I) are deemed novel provided that 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*],4'-piperidine] is not included and thus the present invention also relates to the compounds of formula (I) as defined hereinabove provided that 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*],4'-piperidine] is not included.

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated.

As used herein C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylpropyl, 2-methylbutyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom and the term (=NOH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-4}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-4}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, they may be the same or different.

When any variable (e.g. aryl, R^3, R^4, R^5 etc.) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I) and their prodrugs, *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their prodrugs, *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their prodrugs, *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are

non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

An interesting group of compounds consists of those compounds of formula (I) wherein -A-B- is a bivalent radical of formula -CH=CH-CH=CH- (a-3).

Also interesting compounds are those compounds of formula (I) wherein Z is $-(CH_2)_p-$ (b-1), -CH=CH- (b-2), or $-CH_2-O-$ (b-4).

Other interesting compounds are those compounds of formula (I) wherein L is hydrogen, C_{1-6}alkyl, carboxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyloxycarbonylC_{1-6}alkyl.

Further interesting compounds are those compounds of formula (I) wherein R^1 is hydroxyC_{1-6}alkyl, formyl, C_{1-6}alkyloxycarbonyl, $N(R^3R^4)C(=O)-$, halo or hydrogen.

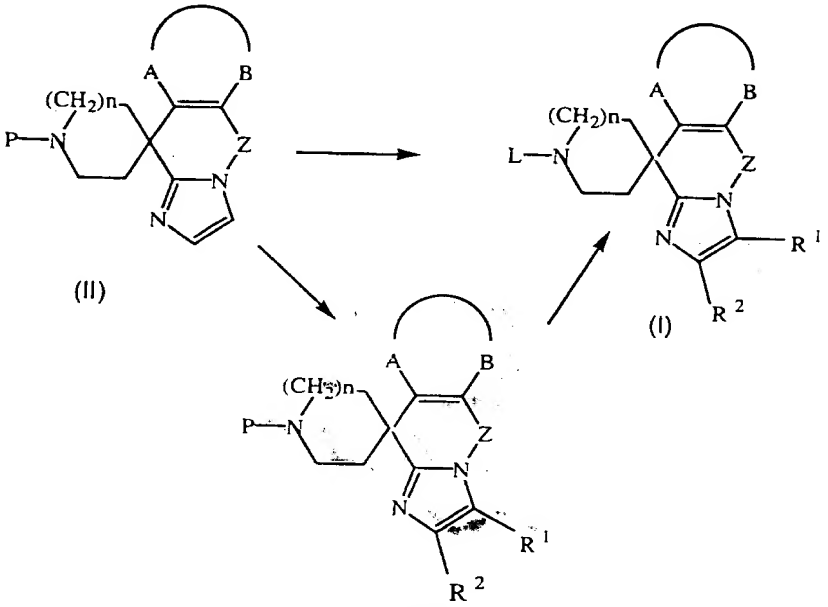
Special compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :
-A-B- is a bivalent radical of formula -CH=CH-CH=CH- (a-3) wherein each hydrogen may independently be replaced by C_{1-6}alkyl, C_{1-6}alkyloxy, halo or hydroxy;
Z is $-(CH_2)_p-$ wherein p is 1,2,3 or 4, $-CH_2-C(=O)-$, $-CH_2-CHOH-$, -CH=CH-, $-CH_2-O-$;
L is hydrogen, C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl;
R^1 is hydrogen, formyl, carboxyl, amide, halo, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with hydroxy, C_{1-6}alkyloxy, -NH-C(=O)-C_{1-6}alkyl, -NH-C(=O)-NH_2, -NH-SO_2-C_{1-6}alkyl;
R^2 is hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, halo, amide.

The most preferred compounds are:
5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide;
5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanol;
5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*],4'-piperidine]; and
1'-butyl-5,6-dihydrospiro[imidazo[2,1-b] [3] benzazepine-11-[11H],4'-piperidine], a prodrug, a *N*-oxide, an addition salt, or a quaternary amine thereof.

Compounds of formula (I), can be prepared by deprotecting an intermediate of formula (II), wherein P is a protecting group, for example, benzyl, or those protective groups mentioned in Chapter 7 of "Protective Groups in Organic Synthesis" by T. Greene and P. Wuyts (John Wiley & Sons, Inc. 1991). Said deprotection reaction can be performed by, for example, catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g.

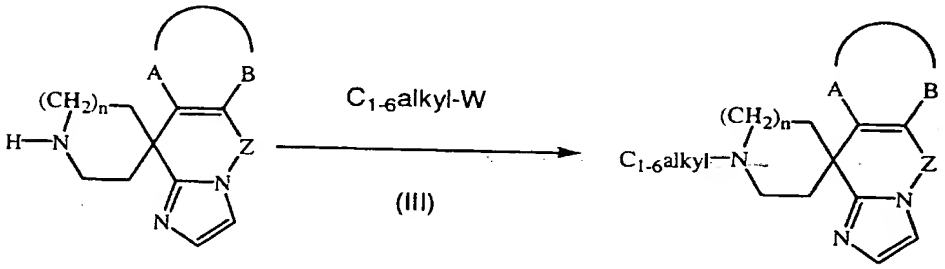
acetic acid and the like. The thus obtained deprotected compounds can optionally further be derivatized either by replacing the hydrogen on the piperidine nitrogen by a moiety belonging to L, or by introducing on the imidazole moiety a R^1 group or a R^1 and R^2 group, or by derivatizing both the piperidine moiety and the imidazole moiety.

An intermediate of formula II can also first be derivatized at the imidazole moiety by introducing a R^1 group or a R^1 and R^2 group, resulting in an intermediate of formula (II-a), and then deprotected, followed optionally by a derivation at the piperidine nitrogen.



(II) (I) (II-a)

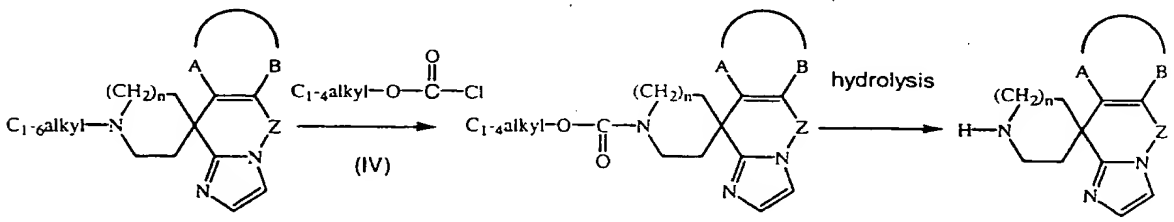
The compounds of formula (I) wherein L is C_{1-6}alkyl and R^1 and R^2 are hydrogen, said compounds being represented by formula (I-a) can be prepared by reacting the compounds of formula (I) wherein L is hydrogen and R^1 and R^2 are hydrogen, said compounds being represented by formula (I-b), with a reagent of formula C_{1-6}alkyl-W (III),wherein W is a suitable leaving group, such as a halo, e.g.chloro, or mesylate, tosylate.



(I-b) (III) (I-a)

Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, an alkanol, a ketone, an ether, a dipolar aprotic solvent, a halogenated hydrocarbon, or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, or an organic base, such as, for example, an amine, may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction.

The compounds of formula (I-a) can be converted into the compounds of formula (I-b) by dealkylating and subsequently carbonylating the compounds of formula (I-a) with a reagent of formula (IV), resulting in compounds of formula (I-c), and subsequently hydrolyzing the thus obtained compounds of formula (I-c).

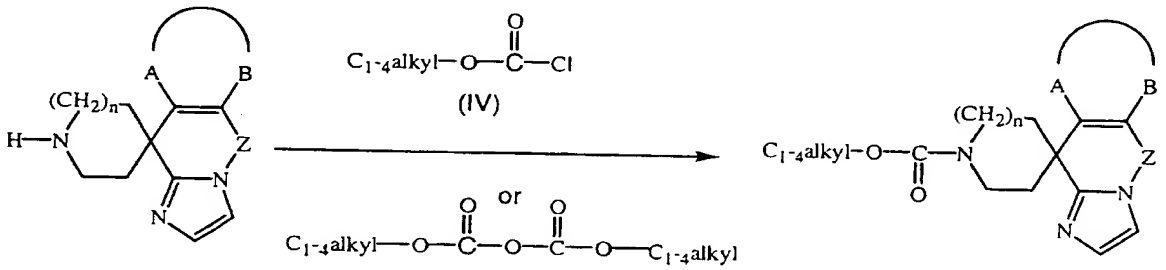


(I-a) (I-c) (I-b)

The reaction with reagent (IV) is conveniently conducted by stirring and heating the starting material with the reagent in an appropriate solvent and in the presence of a suitable base. Appropriate solvents are, for example, aromatic hydro-carbons, e.g. methylbenzene, dimethylbenzene, chlorobenzene; ethers, e.g. 1,2-dimethoxyethane; methylenechloride and the like solvents. Suitable bases are, for example, alkali or earth alkaline metal carbonates, hydrogen carbonates, hydroxides, or organic bases such as, N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, and the like.

The compounds of formula (I-c) are hydrolyzed in acidic or basic media following conventional methods. For example, concentrated acids such as hydrobromic, hydrochloric acid or sulfuric acid can be used, or alternatively bases such as alkali metal or earth alkaline metal hydroxides in water, an alkanol or a mixture of water-alkanol may be used. Suitable alkanols are methanol, ethanol, 2-propanol and the like. In order to enhance the rate of the reaction it is advantageous to heat the reaction mixture, in particular up to the reflux temperature.

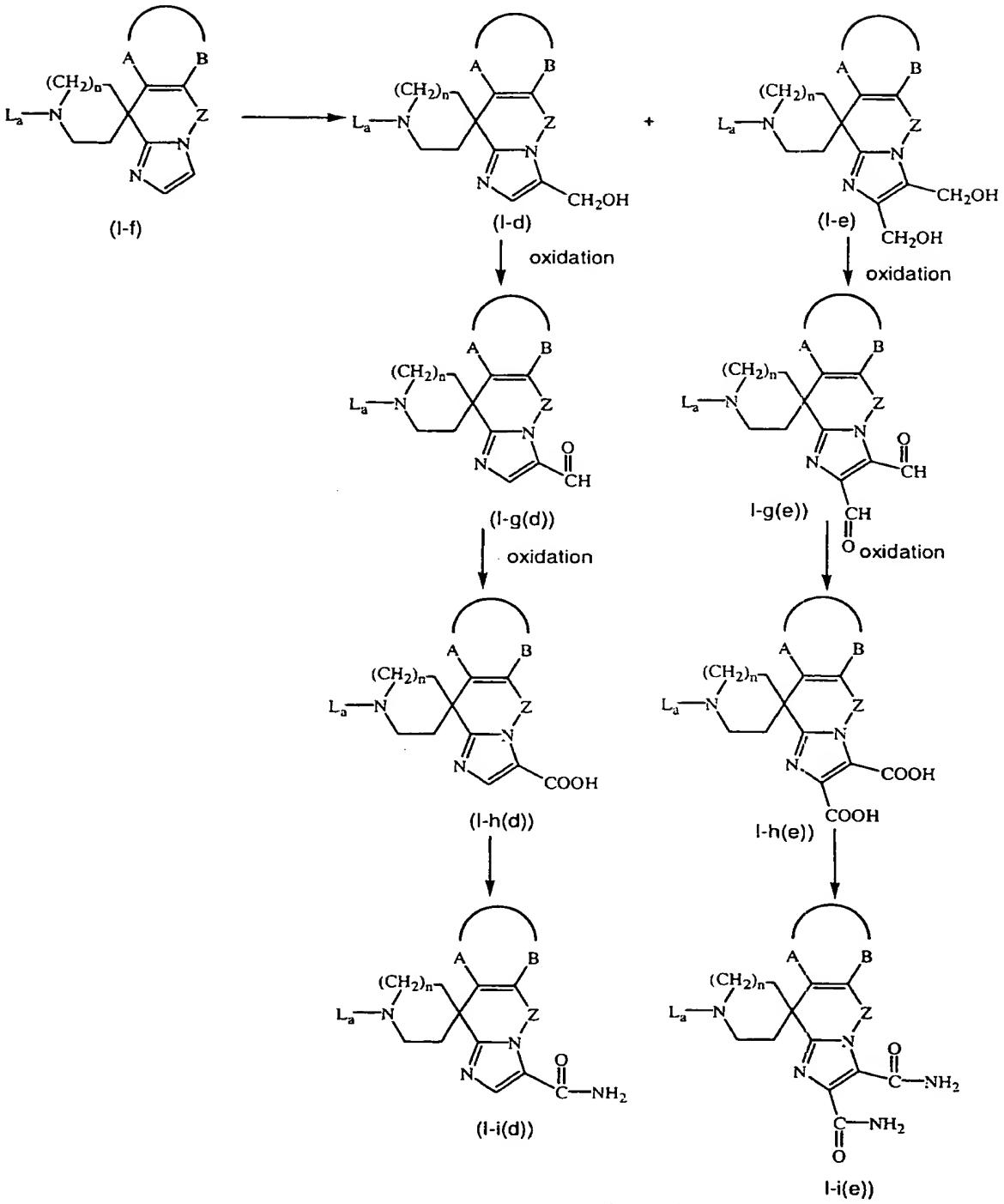
The compounds of formula (I-c), wherein L is C_{1-4}alkyloxycarbonyl, can also be prepared by reacting compounds of formula (I-b) with a reagent of formula (IV) in the presence of a suitable base, e.g. N,N-diethylethanamine, in a reaction inert solvent, e.g. methylenechloride, or by reacting compounds of formula (I-b) with a reagent of formula (IV-1), e.g. t-butyloxyanhydride, in a suitable solvent, such as, e.g. methylenechloride.



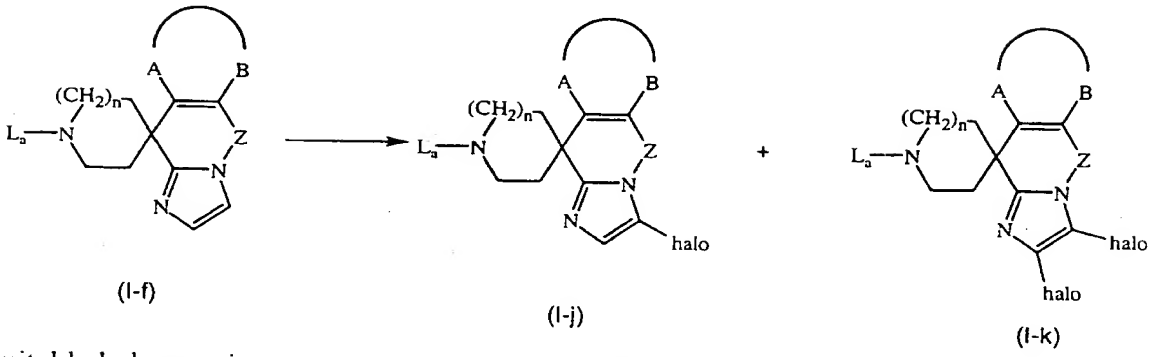
The compounds of formula (I) wherein L is C_{1-6}alkyl or C_{1-4}alkyloxycarbonyl, said L being represented by L_a, and R^1 or R^1 and R^2 represent hydroxymethyl, said compounds being represented by the formula (I-d) and (I-e), can be prepared by reacting the compounds of formula (I) wherein L is L_a and R^1 and R^2 are hydrogen, said compounds being represented by formula (I-f), with formaldehyde, optionally in the presence of an appropriate carboxylic acid - carboxylate mixture such as, for example, acetic acid - sodium acetate and the like. In order to enhance the rate of the reaction, it is advantageous to heat the reaction mixture up to the reflux temperature.

The thus obtained compounds of formula (I-d) and (I-e) can be further oxidized to the corresponding aldehyde, represented by the formula (I-g(d)) and (I-g(e)) or the corresponding carboxylic acid, represented by the formula (I-h(d)) and (I-h(e)), by reaction with a suitable reagent such as, for example, manganese(IV)oxide, respectively, silver nitrate.

The compounds of formula (I-h(d)) and (I-h(e)) can further be converted in the corresponding amide, said compounds being represented by the formula (I-i(d)) and (I-i(e)), by reaction with a suitable carbodiimide, e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in the presence of ammonia and a suitable catalyst, e.g. N,N-dimethylaminopyridine, in a reaction inert solvent, e.g. methylenechloride.

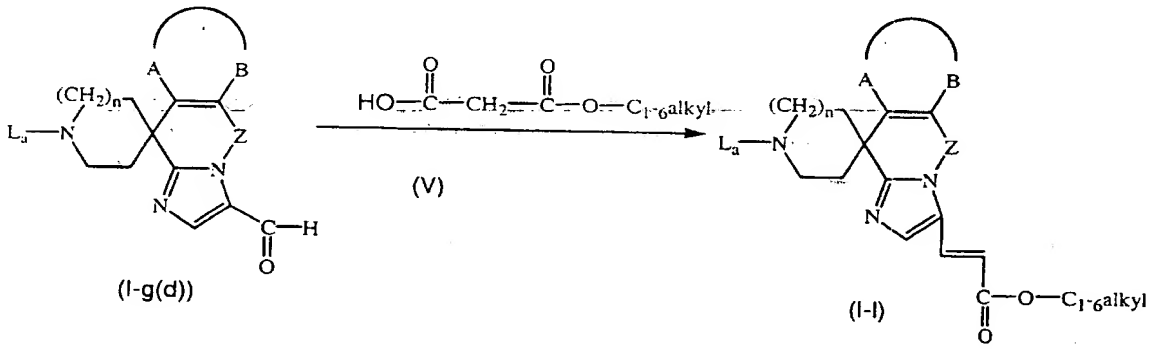


The compounds of formula (I) wherein L is L_a, and R^1 or R^1 and R^2 are halo, said compounds being represented by formula (I-j) and (I-k), can be prepared by halogenating a compound of formula (I-f) with an appropriate halogenating reagent in a reaction-inert solvent.



A suitable halogenating reagent in the above reaction is, for example, an N-halogenated amide, e.g. N-bromosuccinimide. A suitable reaction-inert solvent for said halogenation reaction is, for example, N,N-dimethylformamide, N,N-dimethyl-acetamide, methylenechloride and the like.

The compounds of formula (I) wherein L is L_a and R^1 is C_{1-6}alkyloxycarbonylethenyl, said compounds being represented by the formula (I-l), can be prepared by reacting a compound of formula (I-g(d)) with a reagent of formula (V) in the presence of a base e.g. piperidine, pyridine, and the like.



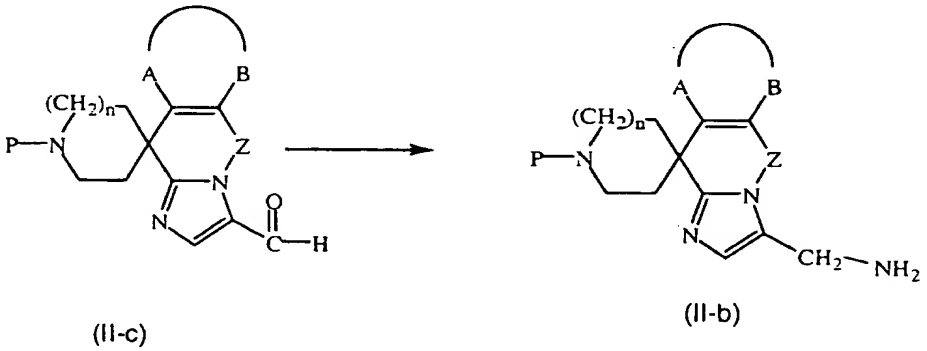
The compounds of formula (I-l) can further be hydrolyzed into a compound of formula (I) wherein R^1 is carboxyethenyl, in the presence of an acid or a base in case L_a is C_{1-6}alkyl, or in the presence of a base, in case L_a is C_{1-4}alkyloxycarbonyl.

The compounds of formula (I) described in the foregoing, wherein L is C_{1-4}alkyloxy-carbonyl and R^1 is other than hydrogen, can optionally be converted into compounds of formula (I) wherein L is hydrogen by reaction with a suitable base or acid. The compounds of formula (I) described in the foregoing, wherein L is C_{1-6}alkyl and R^1 is other than hydrogen, can optionally be converted into compounds of formula (I) wherein L is hydrogen by the procedure described to dealkylate a compound of formula (I-a).

In the foregoing and the following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

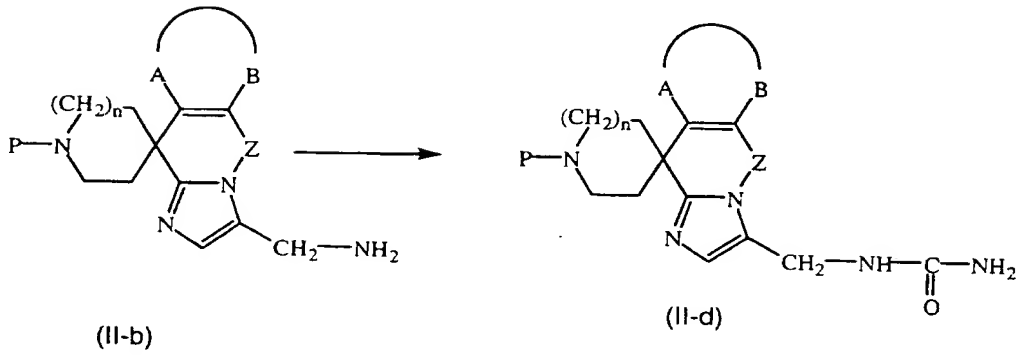
As described hereinabove, the intermediates of formula (II) can be derivatized at the imidazole moiety, said compounds being represented by formula (II-a), before being deprotected.
Introducing R^1 or R^1 and R^2 wherein R^1 and R^2 represent hydroxymethyl, formyl, carboxyl or amide, in a compound of formula (II) can be performed as described herinabove for the preparation of a compound of formula (I-d), (I-e), (I-g(d)), (I-g(e)), (I-h(d)), (I-h(e)), (I-i(d)) and (I-i(e)).

The intermediates of formula (II-a), wherein R^1 is aminomethyl, said compounds being represented by the formula (II-b), can be prepared by reacting an intermediate of formula (II-a) wherein R^1 is formyl, said compounds being represented by formula (II-c) with hydrogen and a mixture of methanol/ammonia in the presence of a suitable catalyst, for example rhodium on alumina, in the presence of a catalyst poison, for example a thiophene solution.



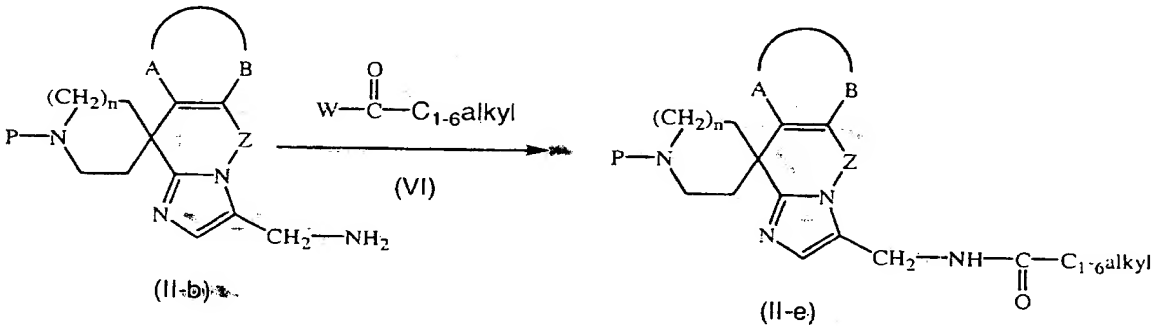
(II-c) (II-b)

The intermediates of formula (II-a), wherein R^1 is $-CH_2NHC(=O)NH_2$, said compounds being represented by the formula (II-d) can be prepared by reacting an intermediate of formula (II-b) with potassium isocyanate in an appropriate acid, such as hydrochloric acid.



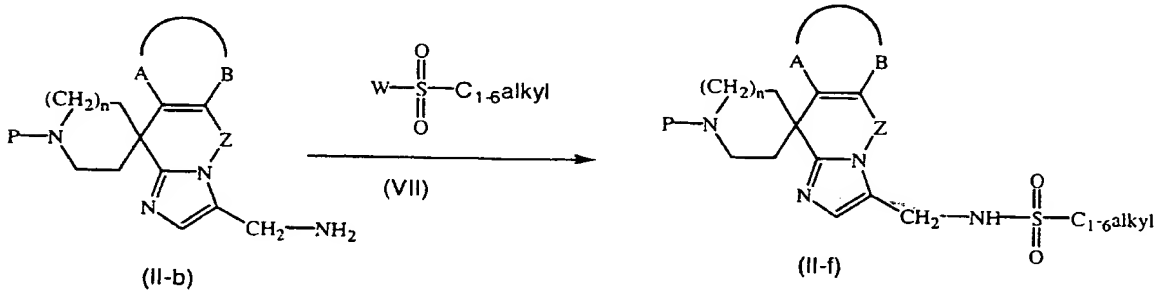
(II-b) (II-d)

The intermediates of formula (II-b) can also be converted in an intermediate of formula (II-a), wherein R^1 is $-CH_2NHC(=O)C_{1-6}alkyl$, said compounds being represented by formula (II-e) by reaction with a reagent of formula (VI), wherein W represents a suitable leaving group, such as a halo atom, for example chloro, in the presence of a suitable base, e.g. N,N-diethylethanamine, in a reaction inert solvent, such as, for example methylenechloride.



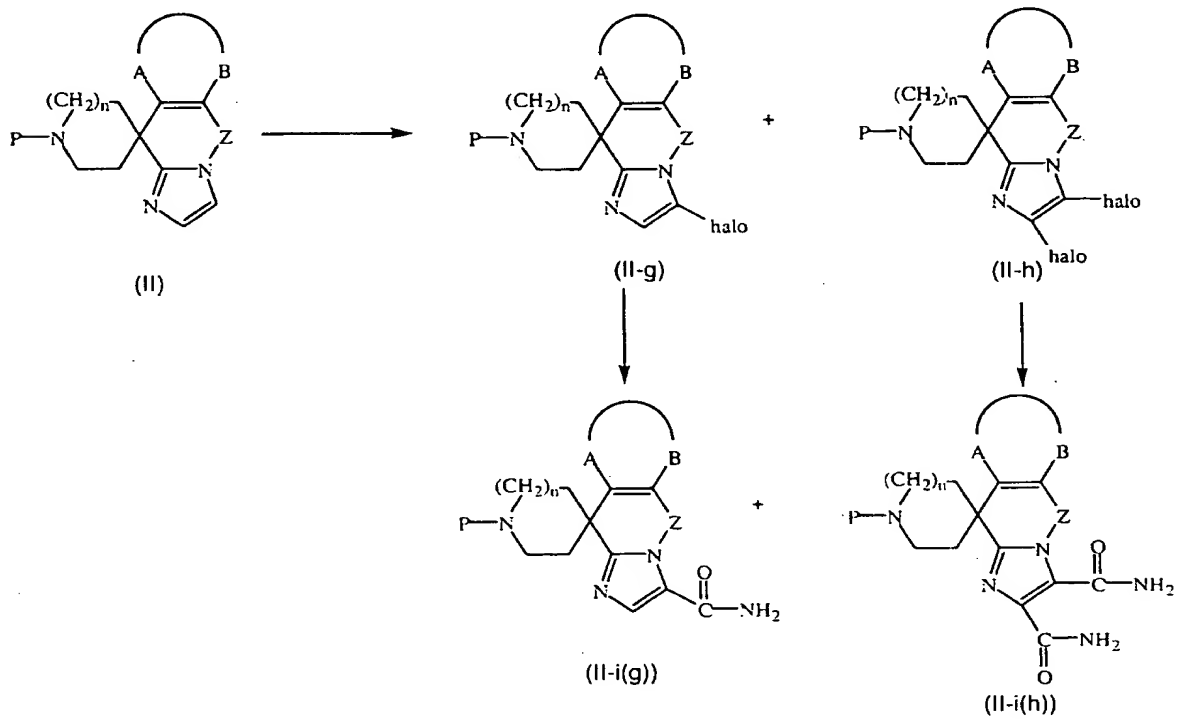
(II-b) (VI) (II-e)

The intermediates of formula (II-b) can further be converted into intermediates of formula (II-a), wherein R^1 is $-CH_2NHS(=O)_2C_{1-6}alkyl$, said compounds being represented by formula (II-f), by reaction with a reagent of formula (VII) wherein W represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, for example N,N-diethylethanamine, in a reaction inert solvent, such as methylenechloride.



(II-b) (VII) (II-f)

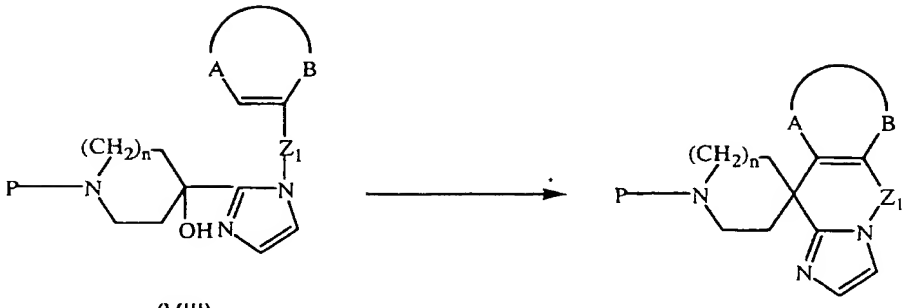
The intermediates of formula (II) can also be halogenated according to the procedure described for the preparation of the compounds of formula (I-j) and (I-k), resulting in an intermediate of formula (II-g) and (II-h).



The intermediates of formula (II-g) and of formula (II-h) can be converted to an intermediate of formula (II-i(g)) and (II-i(h)) by reaction under an atmosphere of ammonia and carbonmonoxide at elevated temperatures in the presence of a suitable catalyst, e.g. acetic acid, palladium salt, and a suitable ligand, e.g. 1.3-bis(diphenylphosphino)propane, in a reaction inert solvent, e.g. tetrahydrofuran.

In the following paragraphs, there are described several methods of preparing the starting materials in the foregoing preparations.

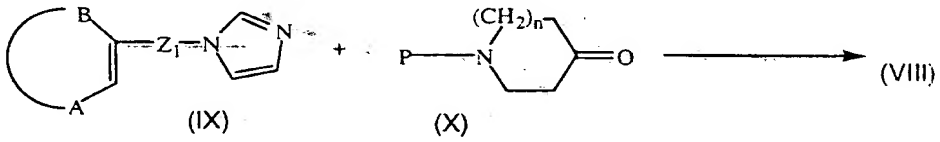
The intermediates of formula (II), wherein Z is a bivalent radical of formula $-(CH_2)_p-$ (b-1), said Z being represented by Z_1, and said intermediates being represented by formula (II-j), can be prepared by cyclizing an alcohol of formula (VIII).



(VIII) (II-j)

Said cyclization reaction is conveniently conducted by treating the intermediate of formula (VIII) with an appropriate acid, thus yielding a reactive intermediate which cyclizes to a compound of formula (II-j). Appropriate acids are, for example, strong acids, e.g. methanesulfonic acid, trifluoroacetic acid, and in particular superacid systems, e.g. trifluoromethanesulfonic acid, or Lewis acids, such as $AlCl_3$ or $SnCl_4$. Obviously, only those compounds of formula II wherein P is stable under the given reaction conditions can be prepared according to the above reaction procedure.

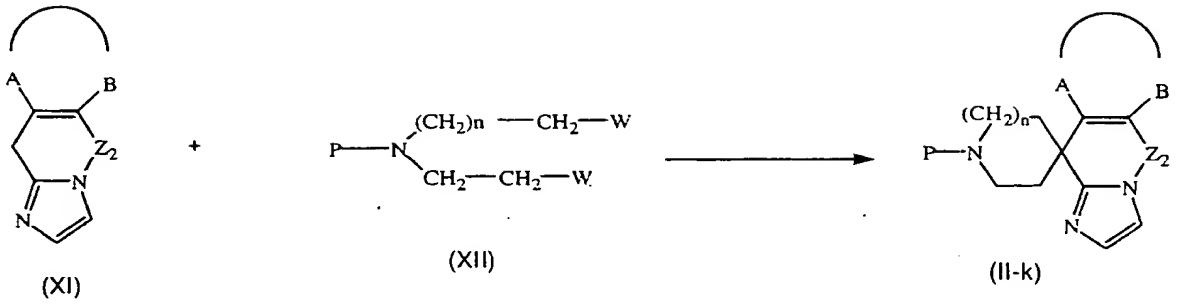
The intermediates of formula (VIII) can be prepared by reacting a imidazole derivative of formula (IX) with a ketone of formula (X):



(IX) (X) (VIII)

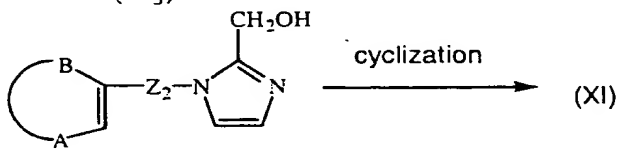
Said reaction is conveniently performed in a reaction inert solvent such as, for example tetrahydrofuran, in the presence of a suitable base such as lithium diisopropylamide and butyl lithium.

The intermediates of formula (II), wherein Z represents a bivalent radical of formula $-(CH_2)_p-$ (b-1), or $-CH_2-O-$ (b-4), said Z being represented by Z_2, and said intermediates being represented by formula (II-k), can also be prepared by reacting a tricyclic moiety of formula (XI) with a reagent of formula (XII) under an inert atmosphere in a reaction inert solvent, such as tetrahydrofuran, in the presence of a suitable base such as, for example, lithium diisopropylamide and butyl lithium.



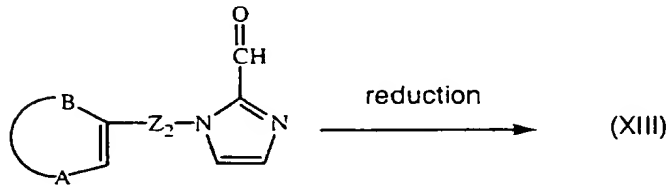
(XI) (XII) (II-k)

The intermediates of formula (XI) can be prepared by cyclizing an intermediate of formula (XIII), according to the procedure for the preparation of intermediates of formula (II-j).



(XIII) (XI)

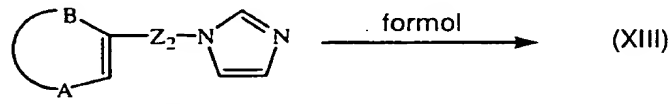
The intermediates of formula (XIII) can be prepared from the corresponding aldehydes, said intermediates being represented by the formula (XIV), by reduction.



(XIV) (XIII)

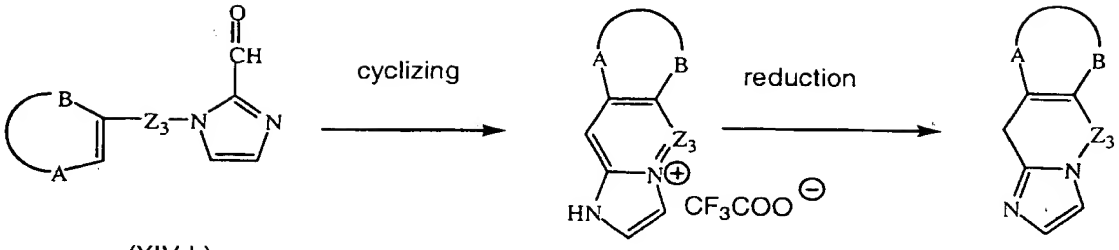
Said reduction can be conducted in a suitable solvent, such as, for example methanol, in the presence of a suitable reducing agent, such as sodium borohydride.

The intermediate of formula (XIII) can also be prepared by reacting an intermediate of formula (XIV-a) with formol 38% solution under pressure.



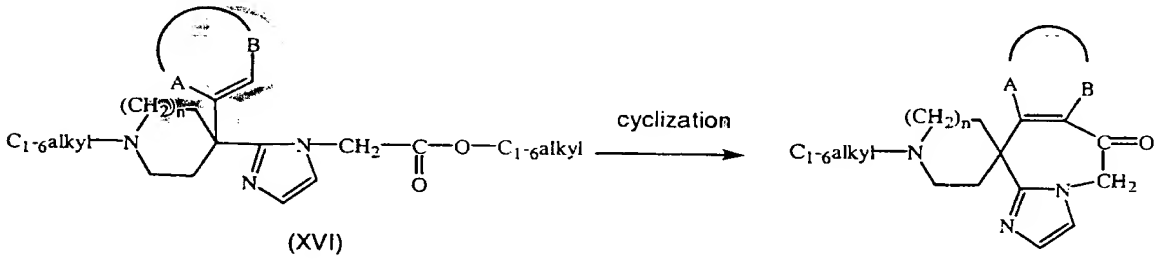
(XIV-a) (XIII)

Alternatively, the tricyclic moieties of formula (XI), wherein Z represents a bivalent radical of formula $-CH_2-$, said Z being represented by Z_3, and said tricylclic moieties being represented by formula (XI-a), may also be prepared by first cyclizing an intermediate of formula (XIV-b), by treating the intermediate of formula (XIV-b) with an appropriate acid, e.g. trifluoroacetic acid, leading to an intermediate of formula (XV), followed by reduction in the presence of a suitable reducing agent.

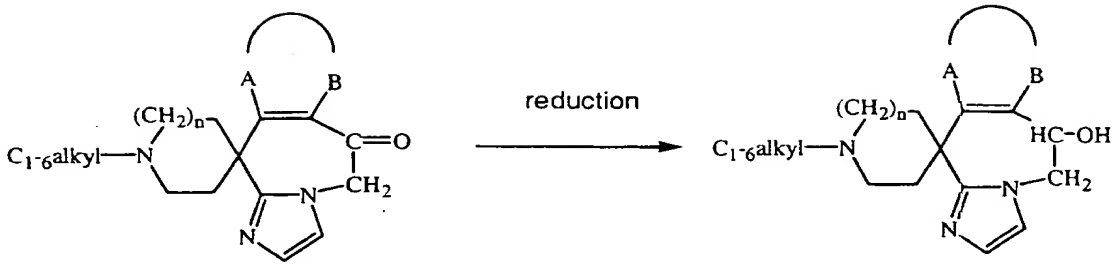


Said reduction reaction can be performed in the presence of hydrogen and an appropriate catalyst in a reaction inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

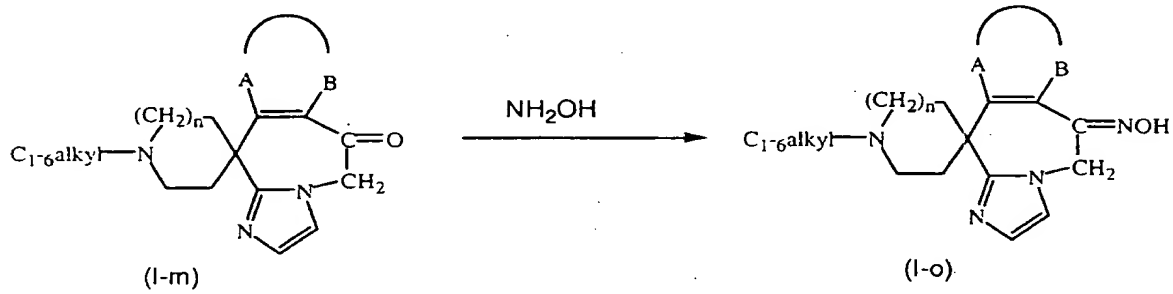
Alternatively, compounds of formula (I), wherein L is C_{1-6}alkyl, Z is a bivalent radical of formula $-CH_2-C(=O)-$ (b-5) and R^1 and R^2 are hydrogen, said compounds being represented by formula (I-m), can be prepared by cyclizing an intermediate of formula (XVI) in the presence of an acid, e.g. trifluoromethanesulfonic acid and the like.



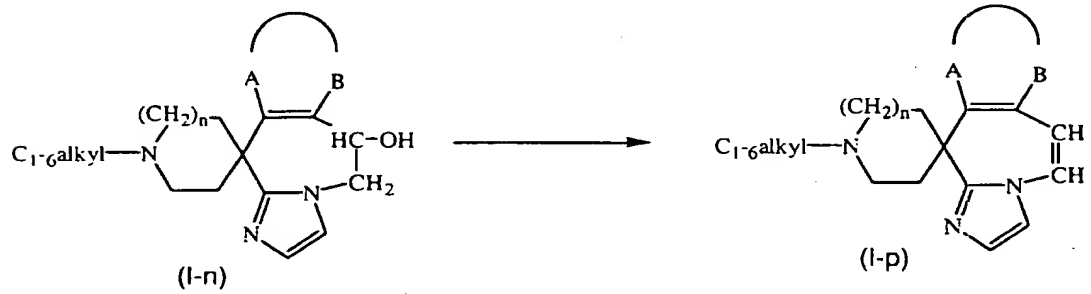
The compounds of formula (I) wherein Z is a bivalent radical of formula $-CH_2-CHOH-$ (b-3), L is C_{1-6}alkyl and R^1 and R^2 are hydrogen, said compounds being represented by the formula (I-n), can be prepared by reacting the compounds of formula (I-m) in the presence of a reducing reagent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. methanol and the like.



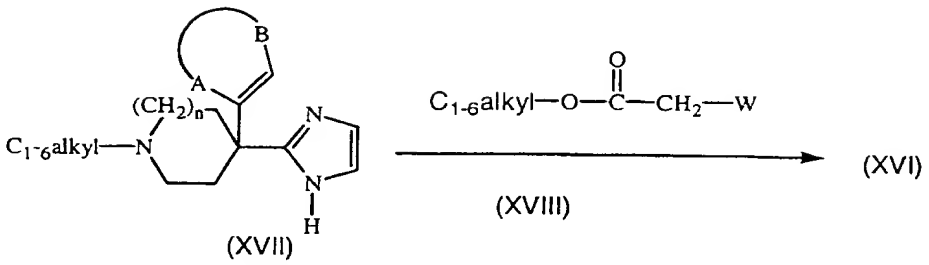
The compounds of formula (I) wherein Z is a bivalent radical of formula -CH_2-C(=N-OH)- (b-6), L is C_{1-6}alkyl and $R^1$and R^2 are hydrogen, said compounds being represented by the formula (I-o), can be prepared by reacting the compounds of formula (I-m) with hydroxylamine or a salt, e.g. the hydrochloride salt, thereof, in a reaction inert solvent, e.g. pyridine and the like.



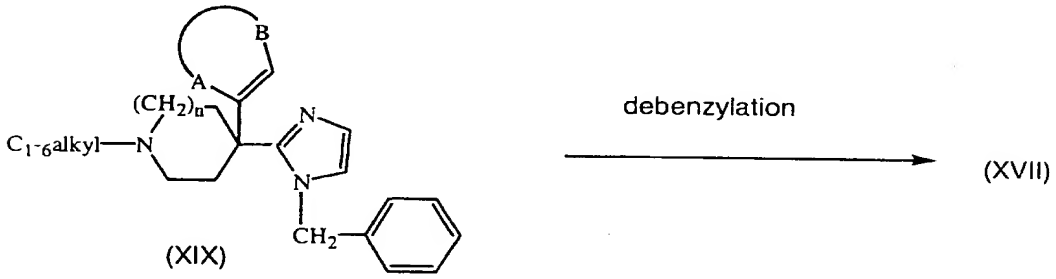
The compounds of formula (I) wherein Z is a bivalent radical of the formula -CH=CH- (b-2), L is C_{1-6}alkyl and $R^1$and R^2 are hydrogen, said compounds being represented by the formula (I-p), can be prepared by reacting the compounds of formula (I-n) in the presence of an acid, e.g. methanesulfonic acid and the like.



The intermediates of formula (XVI) can be prepared by reacting an intermediate of formula (XVII) with a reagent of formula (XVIII), wherein W represents, as described hereinabove, a suitable leaving group, e.g. chloro, in the presence of a suitable base, e.g. sodium hydride, in a reaction inert solvent, e.g. N,N-dimethylformamide and the like.

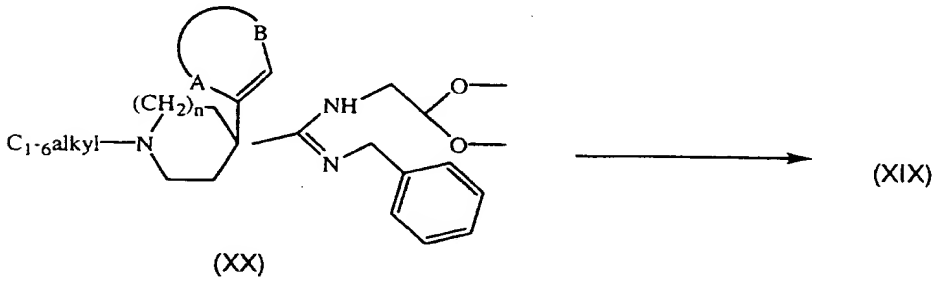


The intermediates of formula (XVII) can be prepared by debenzylating an intermediate of formula (XIX).

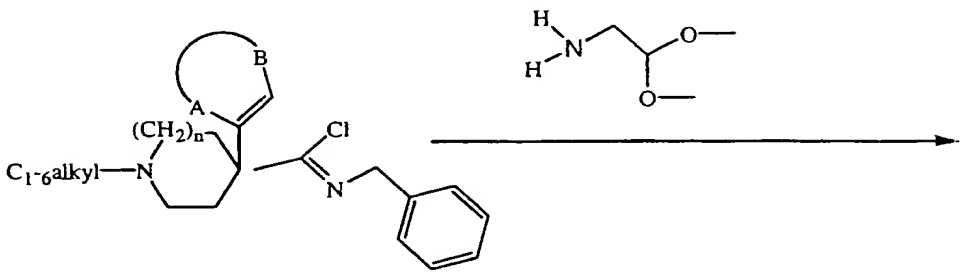


Said debenzylation reaction can be performed by, for example, catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

The intermediates of formula (XIX) can be prepared by imidazole formation out of an intermediate of formula (XX) in an acid, such as hydrochloric acid.

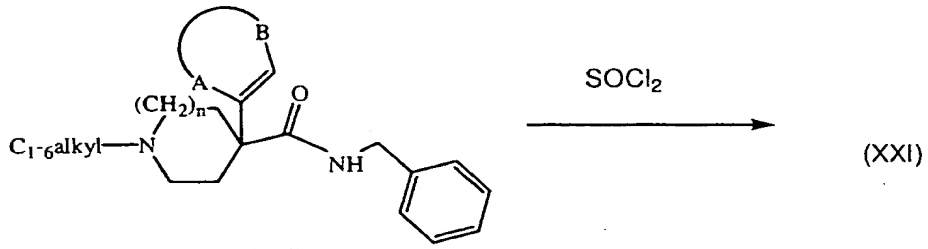


The intermediates of formula (XX) can be prepared by reacting an intermediate of formula (XXI) with 2,2-dimethoxyethylamine in a reaction inert solvent, such as, for example N,N-dimethylformamide and the like.



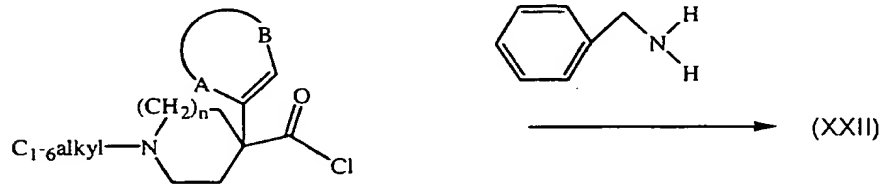
(XXI) (XX)

The intermediates of formula (XXI) can be prepared by reacting an intermediate of formula (XXII) with thionylchloride.



(XXII) (XXI)

The intermediates of formula (XXII) can be prepared by substituting an intermediate of formula (XXIII) with benzylamine in the presence of a suitable base, e.g. N,N-diethyl-ethanamine, in a reaction inert solvent, e.g. methylenechloride and the like.



(XXIII) (XXII)

Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions, comprising those described hereinabove.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-

peroxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to conventional reaction procedures generally known in the art. For example, the preparation of 1-(1-phenyl-ethyl)-1*H*-imidazole is described in WO 92/22551.

The compounds of formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms possess useful pharmacological properties. In particular they are active antihistaminic agents, which activity can be demonstrated by for instance the 'Histamine - induced Lethality in Guinea Pigs' test (Arch. Int. Pharmacodyn. Ther., 251, 39-51, 1981), 'Protection of Rats from Compound 48/80 - induced Lethality' test (Arch. Int. Pharmacodyn. Ther., 234, 164-176, 1978), and 'Ascaris Allergy in Dogs' test (Arch. Int. Pharmacodyn. Ther., 251, 39-51, 1981 and Drug Dev. Res., 8, 95-102, 1986).

Some of the intermediates of formula (II-a) also have interesting pharmacological properties.

The compounds of the present invention have a selective binding affinity for the H_1 receptor, more in particular, they have a very low affinity for the $5HT_{2A}$ serotonin receptor and the $5HT_{2A}$ serotonin receptor. This dissociation between the H_1 receptor binding affinity and the $5HT_{2c}$ and $5HT_{2A}$ receptor binding affinity renders it unlikely for the present compounds to cause appetite stimulation and inappropriate weight gain reported for some other H_1-antagonists.

An important asset of the present compounds is their lack of sedating properties at therapeutic dose levels, a troublesome side effect associated with many antihistaminic and antiallergic compounds. The non-sedating properties of the present compounds can be demonstrated, for example, by the results obtained in studying the sleep - wakefulness cycle of the rat (Psychopharmacology, 97, 436-442, (1989)) and the state of vigilance using EEG power spectra in wake rats (Sleep Research 24A, 118, (1995)).

The compounds of the present invention are also characterized by the absence of relevant cardio-hemodynamic and electrophysiological effects such as QTc prolongation.

An additional advantage of some of the present compounds is that they exhibit little or no metabolic transformations in animal and human liver, thus indicating a low risk for metabolic interactions.

Another interesting feature of the present compounds relates to their fast onset of action and the favorable duration of their action. The latter characteristic may enable the administration of the compound once daily.

The present compounds have a favorable physicochemical profile, particularly in terms of solubility and chemical stability.

In view of their physicochemical and pharmacological properties, the compounds of formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms thereof are very useful in the treatment of a broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, pruritis, allergic asthma and the like.

Also in view of their useful physicochemical and pharmacological properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are, desirably as unitary dosage forms, administered orally, parenterally, percutaneously, rectally or topically for systemic action, or for topical action. In case of oral liquid pharmaceutical preparations, comprising solutions, suspensions, syrups, elixirs and emulsions, any of the usual pharmaceutical media, such as, for example, water, glycols, oils, alcohols and the like, may be employed, whereas in case of oral solid pharmaceutical preparations, comprising powders, pills, capsules and tablets, excipients such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like may be employed. Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms, in which case solid pharmaceutical carriers are obviously employed. In case of injectable pharmaceutical compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, such as semipolair solvents, may be included, for example, to aid solubility. Examples of carriers for injectable solutions comprise saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of the aforementioned formulas may also be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. For the preparation of injectable suspensions, appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment or as a gel. In case of pharmaceutical compositions for rectal administration, any of the usual excipients may be employed, comprising fat based and water soluble excipients, optionally combined with suitable additives, such as suspending or wetting agents. As appropriate compositions for topical application there may be cited all compositions usually

employed for topically administering drugs e.g. creams, gellies, dressings, lotions, shampoos, tinctures, pastes, ointments, salves, ovules, powders, inhalations, nose sprays, eye drops and the like. Semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used, but application of said compositions may be, for example, also by aerosol, e.g. with a propellent such as nitrogen, carbon dioxide, a freon, or without a propellent such as a pump spray or drops.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, suppositories, ovules, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also relates to a method of treating warm-blooded animals suffering from allergic diseases by administering to said warm-blooded animals an effective anti-allergic amount of a compound of formula (I), a prodrug, *N*-oxide, addition salt, quaternary amine or stereochemically isomeric form thereof.

The present invention further relates to the compounds of formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms thereof for use as a medicine, and hence, the use of the present compounds for the manufacture of a medicament for treating warm-blooded animals suffering from allergic diseases is also part of the present invention.

In general it is contemplated that an effective antiallergic amount would be from about 0.001 mg/kg to about 2 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 0.5 mg/kg body weight. In any event, an effective antiallergic amount may depend on the type and severity of the affliction to be treated and the evaluation of the physician prescribing the treatment with the subject drugs.

The following examples are intended to illustrate the scope of the present invention.

Experimental part

Hereinafter, THF means tetrahydrofuran, DIPE means diisopropyl ether, DMF means N,N-dimethylformamide, DIPA means diisopropyl amine

A. Preparation of intermediate compounds

Example A1

a) A mixture of DIPA (1.4 mol) in THF (3000ml) was stirred at -70°C under N_2 flow. Bulithium 2.5 M/hexane (1.3 mol) was added portionwise at a temperature below -40°C. The mixture was stirred at -70°C for 15 min. 1-phenylethyl-1*H*-imidazole (1 mol) dissolved in THF was added dropwise at a temperature below -55°C. The mixture was stirred at -70°C for 1 hour. 1-(phenylmethyl)-4-piperidinone (1.2 mol) dissolved in THF was added dropwise at a temperature below -55°C. The mixture was stirred at -70°C for 1 hour, then brought to room temperature, stirred at room temperature overnight and decomposed with H_2O. The organic solvent was evaporated. The aqueous concentrate was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from DIPE (1100ml). The precipitate was filtered off, washed with DIPE and dried, yielding 271g of 4-[1-(2-phenylethyl)-1*H*-imidazol-2-yl]-1-(phenylmethyl)-4-piperidinol (75%) (interm. 1).

b) A mixture of intermediate (1) (0.75 mol) in trifluoromethanesulfonic acid (1500ml) was stirred at 65°C for 120 hours; then cooled, poured out on ice, alkalized with NaOH 50% and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from DIPE/CH_3CN (99/1) (1200ml). The precipitate was filtered off and dried, yielding 169.6g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] (66%) (interm. 2).

Example A2

1-(phenylmethyl)-4-[1-(phenylmethyl)-1*H*-imidazol-2-yl]-4-piperidinol (0.124 mol) and $AlCl_3$ (0.31 mol) were stirred in a melt at 120°C for 1h. The mixture was cooled, $AlCl_3$ (0.31 mol) was added and the mixture was stirred at 120°C for 1h. The mixture was poured into ice, alkalized with NaOH 50% and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered off and evaporated. The residue was purified by HPLC (eluent : CH_2Cl_2/(CH_3OH/NH_3) 99/1). The pure fractions were collected and evaporated. The residue was converted into the hydrochloric acid salt (1:2) in $(C_2H_5)_2O$, yielding 0.91g of 1'-(phenylmethyl)spiro[imidazo[1,2-b]isoquinoline-10[5H],4'-piperidine]dihydrochloride.dihydrate (2%) (interm. 3; mp. 161.2 °C).

Example A3

a) A mixture of intermediate (2) (0.09 mol) in CH_2Cl_2 (1000ml) was cooled to 0°C. 1-bromo-2,5-pyrrolidinedione (0.09 mol) was added portionwise over a 1-hour period. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5 to 95/5). A pure fraction was collected and the solvent was evaporated. The residue was dissolved in ethanol and converted into the (E)-2-butenedioic acid salt (1:1). The precipitate was filtered off and dried, yielding 17.3g of 3-bromo-5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine (E)-2-butenedioate(1:1) (36%) (interm. 4). Part of this fraction (16.5g) was taken up in H_2O, K_2CO_3 and CH_2Cl_2. The mixture was separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (MgSO4), filtered and the solvent was evaporated, yielding 12.9g of 3-bromo-5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine (interm. 4a).

b) A mixture of intermediate (4a) (0.21 mol), 1,3-propanediylbis[diphenylphosphine] (2.5 g) and acetic acid, palladium(2+) salt (0.68 g) in THF (567 ml) was stirred in an autoclave at 150°C for 16 hours under NH_3 (10 atm) and CO (30 atm). The mixture was filtered and the filtrate was evaporated. This residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/C_2H_5OH 100/0 over 46 min to 70/30). The pure fractions were collected and the solvent was evaporated, yielding 36 g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide (44%) (interm. 5).

Example A4

a) A mixture of intermediate (2) (0.16 mol) and sodium acetate (45g) in formol 38% (300ml) and acetic acid (30ml) was stirred and refluxed for 6 hours, then cooled, poured out on ice and alkalized with a NaOH solution. The precipitate was filtered off and purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The desired fractions were collected and the solvent was evaporated. The residue was triturated in CH_3CN, filtered off and dried, yielding 13g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanol (interm. 6).

b) A mixture of intermediate (6) (0.032 mol) and MnO_2 (65g) in chloroform (250ml) was stirred and refluxed for 2 hours, then cooled, filtered over dicalite and the filtrate was evaporated, yielding 11g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo-[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxaldehyde (interm. 7).

c) A mixture of intermediate (7) (0.0296 mol) in CH_3OH/NH_3 (500ml) was

hydrogenated at 50°C with Rh/Al_2O_3 5% (2g) as a catalyst in the presence of a thiophene solution (2ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding 11g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanamine (interm. 8). Part of this fraction (1g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:3) with 2-propanol/HCl. The mixture was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.8g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanamine hydrochloride (1:3) hydrate (1:1) (interm. 8a).

d) A mixture of intermediate (8) (0.0198 mol) in HCl 1N (50ml) was stirred at 50°C. KOCN (0.023 mol) was added portionwise (4x0.5g). The mixture was stirred at 50°C for 2 hours, then cooled, neutralized with a $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The pure fractions were collected and the solvent was evaporated, yielding 4.3g of *N*-[[5,6-dihydro-1'-(phenylmethyl)spiro-[11*H*-imidazo[2,1-b][3]benzazepin]-3-yl]methyl]methyl]urea (interm. 9)

Example A5

A mixture of intermediate (8) (0.0295 mol) and triethylamine (0.035 mol) in CH_2Cl_2 (140ml) was stirred at room temperature. A solution of acetyl chloride (0.03 mol) in CH_2Cl_2 (10ml) was added dropwise. The mixture was stirred at room temperature for 1 hour and poured out into H_2O. K_2CO_3 (2g) was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. Part of the residue (1.3g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was triturated in DIPE, filtered off and dried, yielding *N*-[[5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidin]-3-yl]methyl]acetamide (interm. 10).

Example A6

A mixture of intermediate (8) (0.012 mol) and triethyl amine (0.015 mol) in CH_2Cl_2 (150ml) was stirred at 0°C under N_2 flow. Methanesulfonyl chloride (0.013 mol) was added dropwise. The mixture was stirred for 2 hours. H_2O was added and the mixture

was extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 2.1g of *N*-[[5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-3-yl]methyl]methanesulfonamide (interm. 11).

Example A7

A mixture of intermediate (31) (Table 1), prepared according to the procedure described in Ex.No. A9d, (0.01 mol) in HBr 48 % solution (60ml) was stirred and refluxed for 2 hours. The solvent was evaporated. The residue was taken up in a small amount of H_2O. The mixture was alkalized with K_2CO_3 and extracted with CH_2Cl_2/CH_3OH. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 4.3g of 5,6-dihydro-1'-(phenylmethyl)spiro[11*H*-imidazo-[2,1-b][3]benzazepine-11,4'-piperidine]-8,9-diol (100%) (interm. 12).

Example A8

1-Methyl-4-phenyl-4-piperidinecarbonyl chloride (0.49 mol) was added portionwise at room temperature to a stirring mixture of benzenemethanamine (0.49 mol) and triethyl amine (1.223 mol) in CH_2Cl_2 (2500ml). The mixture was stirred at room temperature for 1 hour. K_2CO_3 (150g) and H_2O were added. The mixture was stirred and separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 144g of 1-methyl-4-phenyl-*N*-(phenylmethyl)-4-piperidinecarboxamide (95%) (interm. 13).

b) A mixture of intermediate (13) (0.47 mol) in thionylchloride (750ml) was stirred and refluxed for 1 hour. The solvent was evaporated. Toluene was added twice and evaporated again, yielding 190g of *N*-[chloro(1-methyl-4-phenyl-4-piperidinyl)methylene]benzenemethanamine monohydrochloride (100%) (interm. 14).

c) A mixture of intermediate (14) (0.47 mol) in DMF (750ml) was cooled on an ice bath. 2,2-Dimethoxyethanamine (0.54 mol) dissolved in DMF was added dropwise. The mixture was stirred at room temperature overnight. The solvent was evaporated, yielding 210g of *N*-(2,2-dimethoxyethyl)-1-methyl-4-phenyl-*N'*-(phenylmethyl)-4-piperidinecarboximidamide dihydrochloride (100%) (interm. 15).

d) A mixture of intermediate (15) (0.47 mol) in HCl 6N (1500ml) was stirred until a cloudy solution, then washed with CH_2Cl_2 (900ml), stirred at 80°C for 1 hour, cooled, alkalized with a NaOH 50% solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding

38.3g of 1-methyl-4-phenyl-4-[1-(phenylmethyl)-1*H*-imidazol-2-yl]piperidine (25%) (interm. 16).

e) A mixture of intermediate (16) (0.195 mol) in methanol (350ml) was hydrogenated at room temperature for 18 hours with palladium on charcoal 10% (3g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 42.3g of 4-(1*H*-imidazol-2-yl)-1-methyl-4-phenylpiperidine (90%) (interm. 17).

f) A mixture of sodium hydride 60% (0.232 mol) in DMF (150ml) was stirred at room temperature. Intermediate (17) (0.145 mol) dissolved in DMF (400ml) was added dropwise. The mixture was stirred at room temperature for 1 hour. Methyl 2-chloro-acetate (0.232 mol) dissolved in DMF (400ml) was added dropwise. The mixture was stirred at room temperature for 20 min, poured out into a solution of $NaHCO_3$ (20g) in H_2O (2000ml) and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and the solvent was evaporated, yielding 40.1g of methyl 2-(1-metyl-4-phenyl-4-piperidinyl)-1*H*-imidazole-1-acetate (88%) (interm. 18).

Example A9

a) Reaction under N_2 atmosphere. A mixture of DIPA (0.455 mol) in THF (500 ml) was stirred at -78°C. Butyllithium, 2.5M/hexane (0.390 mol) was added dropwise at -40°C. The mixture was stirred for 15 min, then re-cooled to -78°C. A solution of 1-(4-phenylbutyl)-1*H*-imidazole, prepared according to the procedure described in J. Chem. Soc., Perkin Trans., 1 (1975), 17, 1670-1671, (0.325 mol) in THF (350 ml) was added dropwise at -60°C. The mixture was stirred for one hour, then re-cooled to -78°C. This mixture was added dropwise to a mixture of *N*,*N*-dimethylformamide (0.390 mol, dry, p.a.) in THF (500 ml), stirred at -78°C. The reaction mixture was stirred for one hour at -78°C, then allowed to warm to room temperature while stirring overnight. A saturated aqueous NH_4Cl solution (400 ml) was added and this mixture was extracted with THF. The separated organic layer was dried, filtered and the solvent evaporated, yielding 74.2 g of 1-(4-phenylbutyl)-1*H*-imidazole-2-carboxamide (interm. 19).

b) A mixture of intermediate (19) (0.325 mol) in methanol (1400 ml) was stirred at room temperature. $NaBH_4$ (0.650 mol) was added portionwise and the reaction mixture was stirred for 2 hours at room temperature. The solvent was evaporated. The residue was taken up into water and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified

by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, 99/1, 97/3, 96/4, 95/5 and 93/7). The desired fractions were collected and the solvent was evaporated, yielding 49.5 g of 1-(4-phenylbutyl)-1*H*-imidazole-2-methanol (66%) (interm. 20).

c) A mixture of intermediate (20) (0.417 mol) in methanesulfonic acid (960ml) was stirred at 120°C for 40 hours, then cooled, poured out on ice and alkalized with NH_4OH. The organic layer was separated, dried, filtered and the solvent evaporated. This fraction was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). A pure fraction was collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 15.7g of 6,7,8,13-tetrahydro-5*H*-imidazo[2,1-b][3]benzazonine (18%) (interm. 21).

d) A mixture of DIPA (0.151 mol) in THF (650ml) was stirred at -78°C under N_2 flow. Butyllithium 2,5M in hexane (0.144 mol) was added dropwise at a temperature below -40°C. The mixture was stirred at -78°C for 15 min. Intermediate (21) (0.072 mol) in a small amount of THF was added dropwise at a temperature below -55°C. The mixture was stirred at -78°C for 1 hour. *N,N*-bis(2-chloroethyl)benzenemethanamine hydrochloride in a small amount of THF was added dropwise at a temperature below -50°C. The mixture was stirred at -78°C for 1 hour, allowed to warm to room temperature overnight and decomposed with H_2O. The organic solvent was evaporated. The aqueous concentrate was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. This fraction was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, 99/1, 98/2, 96/4, 94/6 and 92/8). A fraction was collected and the solvent was evaporated, yielding 5,6,7,8-tetrahydro-1'-(phenylmethyl)spiro[13*H*-imidazo[2,1-b] [3]benzazonine-13,4'-piperidine] (interm. 22).

Example A10

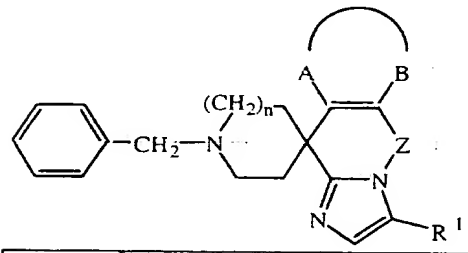
A mixture of 5,10-dihydro-imidazo[1,2-b]isoquinoline-7,8-diol, obtained according to the procedure described in Ex.No. A9 c, (0.155 mol), phenyltrimethylammonium chloride (0.31 mol) and K_2CO_3 (0.68 mol) in DMF (400ml) was stirred at 90°C for 20 hours, cooled, poured out into H_2O and filtered over dicalite. The filtrate was separated into its layers. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 100/0 to 97/3). The pure fractions were collected and the solvent was evaporated, yielding 3g of 5,10-dihydro-7,8-dimethoxyimidazo[1,2-b]isoquinoline (8.4%) (interm. 23).

Example A11

A mixture of compound (22) (0.0117 mol) and triethyl amine (0.0421 mol) in toluene (100ml) was stirred and refluxed. Ethyl carbonochloridate (0.0702 mol) was added dropwise at reflux temperature. The mixture was stirred and refluxed for 1 hour, cooled, poured out into H_2O and K_2CO_3 (15g) and separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ethanol 96/4). The pure fractions were collected and the solvent was evaporated. The residue was boiled in DIPE. The precipitate was filtered off and dried, yielding 2.4g of [1'-(ethoxycarbonyl)spiro[11*H*-imidazo[2,1-b]-[3]benzazepine-11,4'-piperidine)-6-yl] ethyl carbonate (33%) (interm. 24).

Table 1 lists intermediates which were prepared according to one of the above mentioned examples.

Table 1



Interm. No.	Ex. No.	n	z	R1	-A-B-
25	A9d	2	-$(CH_2)_2$-	H	-CH=CH-CH=CH-
3	A2	1	-CH_2-	H	-CH=CH-CH=CH-
2	A1b	1	-$(CH_2)_2$-	Br	-CH=CH-CH=CH-
26	A9d	11	-$(CH_2)_2$-	H	-CH=CF-CH=CH-
27	A9d	1	-$(CH_2)_2$-	H	-CH=CH-CH=CCH_3-
28	A9d	1	-$(CH_2)_3$-	H	-CH=CH-CH=CH-
29	A9d	1	-$(CH_2)_2$-	H	-COH=CH-CH=CH-
30	A9d	1	-$(CH_2)_2$-	H	-CH=CH-COH=CH-
31	A9d	1	-$(CH_2)_2$-	H	-CH=$COCH_3$-$COCH_3$=CH-
32	A9d	1	-O-CH_2-	H	-CH=CH-CH=CH-
12	A7	1	-$(CH_2)_2$-	H	-CH=COH-COH=CH-
6	A4a	1	-$(CH_2)_2$-	CH_2OH	-CH=CH-CH=CH-
7	A4b	1	-$(CH_2)_2$-	C(=O)H	-CH=CH-CH=CH-

Interm. No.	Ex. No.	n	z	R1	-A-B-
8	A4c	1	$-(CH_2)_2-$	CH_2NH_2	-CH=CH-CH=CH-
10	A5	1	$-(CH_2)_2-$	$CH_2NHC(=O)CH_3$	-CH=CH-CH=CH-
9	A4d	1	$-(CH_2)_2-$	$CH_2NHC(=O)NH_2$	-CH=CH-CH=CH-
5	A3b	1	$-(CH_2)_2-$	$C(=O)NH_2$	-CH=CH-CH=CH-
22	A9d	1	$-(CH_2)_4-$	H	-CH=CH-CH=CH-
11	A6	1	$-(CH_2)_2-$	$CH_2NHSO_2CH_3$	-CH=CH-CH=CH-
33	A9d	1	$-(CH_2)-$	H	$-CH=COCH_3-COCH_3=CH-$

B. Preparation of final compounds

Example B1

A mixture of intermediate (2) (0.02 mol) in methanol (150ml) was hydrogenated with palladium on charcoal 10% (2g) as a catalyst at 50°C for 18hours. After uptake of H_2 (1eq), the catalyst was filtered and the filtrate was evaporated, yielding 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] (comp. 6). This fraction was converted into the hydrochloric acid salt (1:1) in CH_3CN, yielding 5g of 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*],4'-piperidine] monohydrochloride (86%) (comp. 6a). A fraction obtained in said way, can also be converted into the (E)-2-butenedioic acid salt.

Example B2

a) A mixture of compound (6) (0.1 mol) and N,N-diethylethanamine (0.13 mol) in CH_2Cl_2 (300ml) was stirred at a temperature below 10°C. Ethyl carbonochloridate (0.12 mol) was added dropwise at this temperature. The mixture was allowed to warm to room temperature and then stirred at room temperature for 1 hour. Water and K_2CO_3 (10g) were added. The mixture was separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 35.4g of ethyl 5,6-dihydrospiro[11*H*-imidazo-[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (100%) (comp. 4).

b) A mixture of compound (4) (0.1 mol), sodium acetate (0.3 mol) and acetic acid (0.258 mol) in formaldehyde 38% solution (165ml) was stirred and refluxed for 10 hours. The mixture was poured out into ice and a NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ethanol 95/5 to 90/10). The pure fractions were collected and the solvent was evaporated, yielding 16.5g of ethyl 5,6-dihydro-3-

(hydroxymethyl)spiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidine]-1'-carboxylate (46%) (comp. 5).

c) A mixture of compound (5) (0.046 mol) and potassium hydroxide (0.46 mol) in 2-propanol (130ml) was stirred and refluxed for 7 hours. The solvent was evaporated. The residue was taken up in water and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 11.5g of 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanol (88%) (comp. 18). Part of this fraction (1g) was dissolved in CH_3OH and converted into the (E)-2-butenedioic acid salt (2:1). The precipitate was filtered off and dried, yielding 0.6g of 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanol (E)-2-butenedioic acid salt (2:1) (comp. 18a).

Example B3

A mixture of compound (6) (0.01 mol) and $(CH_2O)_n$ (0.066 mol) in methanol (150ml) and thiophene 4% solution (1ml) was hydrogenated with palladium on charcoal 10% (1g) as a catalyst at 50°C. After uptake of H_2 (1eq), the catalyst was filtered and the filtrate was evaporated. The residue was taken up in $H_2O/K_2CO_3/NH_4OH$ and stirred. The mixture was extracted with CH_2Cl_2, dried, filtered and evaporated. The residue was converted into the cyclohexanesulfamic acid salt (1:2) in 2-propanone and recrystallized twice from 2-propanol, yielding 2.44g of 6,11-dihydro-1'-methylspiro[5*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] cyclohexylsulfamate(1:2) (40%) (comp. 1).

Example B4

A mixture of 1-bromobutane (0.012 mol), compound (6) (0.01 mol), Na_2CO_3 (0.02 mol) and potassium iodide (few crystals) in 2-butanone (200ml) was stirred and refluxed overnight. The mixture was evaporated, the residue was taken up in water and extracted with CH_2Cl_2. The organic layer was dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and evaporated. The residue was converted into the hydrochloric acid salt (1:2) in 2-propanol. The precipitate was filtered and dried, yielding 0.7g of 1'-butyl-5,6-dihydrospiro[imidazo[2,1-b][3]-benzazepine-11-[11*H*],4'-piperidine] dihydrochloride.hemihydrate (18%) (comp. 3).

Example B5

Bis(1,1-dimethylethyl) dicarbonate (0.095 mol) dissolved in a small amount of CH_2Cl_2 was added dropwise to a stirring mixture of compound (6) (0.079 mol) in CH_2Cl_2 (250ml). The mixture was stirred at room temperature for the weekend, then washed with H_2O, dried, filtered and the solvent was evaporated. Toluene was added and

evaporated again. The residue was stirred in DIPE. The precipitate was filtered off and the filtrate was evaporated. This fraction was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 100/0, 99/1, 98/2 and 96/4). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane. The precipitate was filtered off and dried, yielding 15.05g of 1,1-dimethylethyl 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (54%) (comp. 7).

Example B6

a) A mixture of compound (9) (0.155 mol), prepared according to the procedure described in Ex. No. B2 b, and MnO_2 (300g) in chloroform (1200ml) was stirred and refluxed for 90 min. The mixture was filtered over dicalite and the filtrate was evaporated. Part of this fraction (1g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.5g of 1,1-dimethylethyl 3-formyl-5,6-dihydrospiro[imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (comp. 12).

b) A mixture of compound (12) (0.134 mol), MnCN (0.705 mol) and MnO_2 (233g) in methanol (2500ml) was stirred at room temperature. Acetic acid (45.5ml) was added dropwise. The mixture was stirred and refluxed for 20 hours and filtered over dicalite. The filtrate was evaporated. The residue was taken up in H_2O, CH_2Cl_2 and K_2CO_3. The mixture was separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). A pure fraction was collected and the solvent was evaporated, yielding 47.7g of methyl (1,1-dimethylethyl) 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3,1'-dicarboxylate (87%) (comp. 13).

c) A mixture of compound (13) (0.056 mol) in NaOH 1N (100ml), H_2O (250ml) and THF (250ml) was stirred at room temperature for 18 hours. The organic solvent was evaporated. The aqueous concentrate was neutralized with HCl 1N (100ml) and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Part of this fraction (2g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 1.16g of 1'-[(1,1-dimethylethoxy)-carbonyl]-5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxylic acid (comp. 14).

d) A mixture of compound (14) (0.04 mol) and *N*,*N*-dimethyl-4-pyridinamine (0.04 mol) in CH_2Cl_2 (300ml) was stirred until complete dissolution. N,N-diethylethanamine (0.05 mol) was added. Then *N'*-(ethylcarbonimidoyl)-*N*,*N*-dimethyl-1,3-propanediamine monohydrochloride (0.05 mol) was added portionwise. The mixture was stirred at room temperature for 30 min. N,N-diethylethanamine (0.06 mol)

was added and then NH_4Cl (0.05 mol) was added portionwise. The mixture was stirred at room temperature overnight, poured out into H_2O and separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 9.5g of 1,1-dimethylethyl 3-(aminocarbonyl)-5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (60%) (comp. 16).

e) A mixture of compound (16) (0.023 mol) in HCl/2-propanol (25ml) and methanol (100ml) was stirred and refluxed for 90 min and then cooled. The precipitate was filtered off and dried, yielding 8g of 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidine]-3-carboxamide dihydrochloride (94%) (comp. 17). The precipitate can also be converted into the (E)-2-butenedioic acid salt.

Example B7

a) A solution of compound (7) (1.63 mol) in CH_2Cl_2 (7500ml) was cooled to 0°C under N_2 flow. 1-Bromo-2,5-pyrrolidinedione (1.63 mol) was added portionwise (29g each). H_2O (3000ml) was added. The mixture was stirred overnight. The organic layer was separated, dried, filtered and the solvent was evaporated. This fraction was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, 98/2, 90/10 and 100/0). A pure fraction was collected and the solvent was evaporated, yielding 189g of 1,1-dimethylethyl 2,3-dibromo-5,6-dihydrospiro[11H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (27%) (comp. 48). The monobromo analogue can be prepared in a similar way.

b) A mixture of compound (48) (0.02 mol), Acetic acid, palladium(2+) salt (0.15g) and 1,3-propanediylbis[diphenylphosphine] (0.55g) in THF (150ml) was stirred in an autoclave at 150°C for 16 hours under pressure of CO gas (30 bar) and NH_3 gas (10 atm). The mixture was cooled, filtered and the filtrate was evaporated. This fraction was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 1,1-dimethylethyl 2,3-bis(aminocarbonyl)-5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (comp. 49).

Example B8

Dibenzoyl peroxide (0.5g) was added to a stirring mixture of compound (7) (0.039 mol) in CH_2Cl_2 (210ml). 1-Chloro-2,5-pyrrolidinedione (0.078 mol) in a small amount of

CH_2Cl_2 was added dropwise. The mixture was stirred at room temperature overnight. The solvent was evaporated. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ CH_3OH 100/0, 99/1, 98/2, 96/4 and 94/6). The pure fractions were collected and the solvent was evaporated. Some starting material (7.5g; 0.02 mol) was recuperated. The reaction was carried out again. Dibenzoyl peroxide (0.5g) was added to a stirring mixture of compound (7) (0.02 mol) in CH_2Cl_2 (210ml). 1-Chloro-2,5-pyrrolidinedione (0.078 mol) in a small amount of CH_2Cl_2 was added dropwise. The mixture was stirred at room temperature overnight. The solvent was evaporated. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 100/0, 99/1 and 98.5/1.5). The pure fractions were collected and the solvent was evaporated. The residue was combined with the one obtained from the first reaction, yielding 14g of 1,1-dimethylethyl 3-chloro-5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate (93%) (comp. 19).

Example B9

a) A mixture of intermediate (18) (0.152 mol) in trifluoromethanesulfonic acid (500ml) was stirred at 158°C for 90 hours. The mixture was cooled, poured out on ice and K_2CO_3 (800g) and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated partially until 100ml while the temperature was kept below 40°C. The concentrate was purified immediately by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The pure fractions were collected and the solvent was evaporated, yielding 18.1g of 1-methylspiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-6(5*H*)-one (42%) (comp. 22). Part of this fraction (1.5g) was dissolved in ethanol and converted into the (E)-2-butenedioic acid salt (2:3). The precipitate was filtered off and dried, yielding 1.92g of 1-methylspiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-6(5*H*)-one (E)-2-butenedioic acid salt (2:3) (comp. 22a).

b) A mixture of intermediate (24) (0.041 mol) in HBr 48% solution (250ml) was stirred and refluxed for 4 hours. The mixture was poured out on ice and K_2CO_3 and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 10.4g of spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-6(5*H*)-one (95%) (comp. 23). Part of this fraction (0.9g) was dissolved in ethanol and converted into the (E)-2-butenedioic acid salt (2:3). The precipitate was

filtered off and dried, yielding 0.78g of spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidin]-6(5*H*)-one (E)-2-butenedioic acid salt (2:3) (comp. 23a).

c) A mixture of compound (23) (0.01 mol) in methanol (300ml) was stirred on an ice bath. $NaBH_4$ (0.02 mol) was added portionwise over a 15-min period. The mixture was stirred on an ice bath for 1 hour. The solvent was evaporated at a temperature below 40°C. The residue was taken up in H_2O and the mixture was extracted with CH_2Cl_2/CH_3OH 90/10. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 2g of 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]-benzazepine-11,4'-piperidine]-6-ol (75%) (comp. 26).

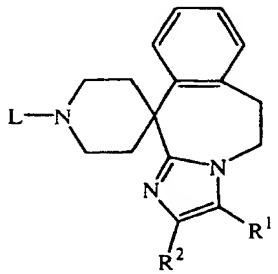
d) A mixture of compound (26) (0.0075 mol) in methanesulfonic acid (50ml) was stirred at room temperature for 40 min. The mixture was poured out on ice, alkalized with a NaOH 50% solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 2g of spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] (100%) (comp.27). Part of this fraction (0.3g) was dissolved in ethanol and converted into the (E)-2-butenedioic acid salt (1:1). The precipitate was filtered off and dried, yielding 0.26g spiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] (E)-2-butenedioic acid salt (1:1) (comp. 27a).

Example B10

A mixture of compound (24) (0.0128 mol) in H_2SO_4 (5ml) and methanol (100ml) was stirred and refluxed for the weekend. The solvent was evaporated. The residue was taken up in H_2O. The mixture was alkalized with a NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 4.4g of 5,6-dihydro-2,3-bis(methoxymethyl)spiro[11H-imidazo-[2,1-b][3]benzazepine-11,4'-piperidine] (100%) (comp. 31).

The following Tables list compounds of formula (I) as prepared according to one of the above examples (Ex. No.).

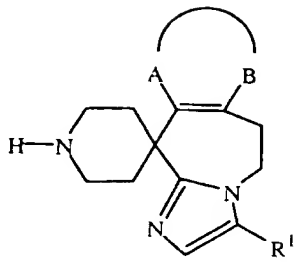
Table 2



Co. No.	Ex. No.	R_1	R_2	L	Salt
1	B3	H	H	CH_3	(1)
3	B4	H	H	$CH_2CH_2CH_2CH_3$	
4	B2a	H	H	$C(=O)OCH_2CH_3$	
5	B2b	CH_2OH	H	$C(=O)OCH_2CH_3$	
6	B1	H	H	H	
6a	B1	H	H	H	(2)
7	B5	H	H	$C(=O)OC(CH_3)_3$	
9	B2b	CH_2OH	H	$C(=O)OC(CH_3)_3$	
10	B2b	CH_2OH	CH_2OH	$C(=O)OC(CH_3)_3$	
12	B6a	C(=O)H	H	$C(=O)OC(CH_3)_3$	
13	B6b	$C(=O)OCH_3$	H	$C(=O)OC(CH_3)_3$	
14	B6c	C(=O)OH	H	$C(=O)OC(CH_3)_3$	
15	B6e	$C(=O)OCH_3$	H	H	
15a	B6e	$C(=O)OCH_3$	H	H	(3)
16	B6d	$C(=O)NH_2$	H	$C(=O)OC(CH_3)_3$	
17	B6e	$C(=O)NH_2$	H	H	(2)
18	B2c/B6e	CH_2OH	H	H	
18a	B2c	CH_2OH	H	H	(4)
19	B8	Cl	H	$C(=O)OC(CH_3)_3$	
20	B6e	Cl	H	H	(3)
24	B6e	CH_2OH	CH_2OH	H	
31	B10/B6e	CH_2OCH_3	CH_2OCH_3	H	
35	B1	$CH_2NHC(=O)CH_3$	H	H	
39	B1	$CH_2NHC(=O)NH_2$	H	H	
41	B1	$C(=O)NH_2$	H	H	
43	B1	$CH_2NHSO_2CH_3$	H	H	
48	B7a	Br	Br	$C(=O)OC(CH_3)_3$	
49	B7b	$C(=O)NH_2$	$C(=O)NH_2$	$C(=O)OC(CH_3)_3$	
51	B6e	CH_2OCH_3	CH_2OH	H	
52	B6e	CH_2OH	CH_2OCH_3	H	
53	B6e	$C(=O)NH_2$	$C(=O)NH_2$	H	(2)

(1) cyclohexylsulfamate (1:2); (2) hydrochloric acid salt (1:2); (3) (E)-2-butenedioate (1:1); (4) (E)-2-butenedioate (2:1)

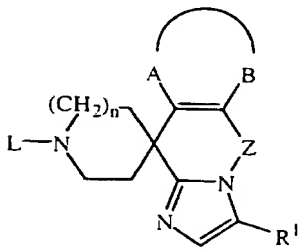
Table 3



Co No.	Ex. No.	R_1	-A-B-	Salt
8	B1	H	-CH=CF-CH=CH-	(5)
11	B1	H	-CH=CH-CH=CCH$_3$-	
21	B1	H	-CH=C(OH)-CH=CH-	
29	B1	H	-C(OH)=CH-CH=CH-	
30	B1	H	-CH=CH-C(OH)=CH-	
32	B1	H	-CH=C(OCH$_3$)-C(OCH$_3$)=CH-	
32a	B1	H	-CH=C(OCH$_3$)-C(OCH$_3$)=CH-	(6)
34	B1	H	-CH=C(OH)-C(OH)=CH-	
46	B6e	CH_2OH	-CH=C(OCH$_3$)-C(OCH$_3$)=CH-	
50	B6e	Cl	-CH=C(OCH$_3$)-C(OCH$_3$)=CH-	
54	B2c	H	-CH=CH-S-	
55	B1	H	-CH=CH-N(CH$_3$)-	

(5) hydrochloric acid salt (1:1); (6) (E)-2-butenedioate (2:3)

Table 4



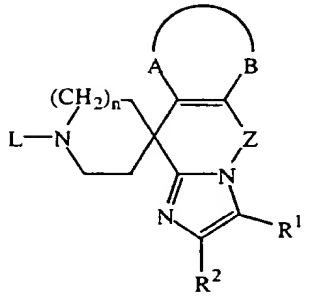
Co. No.	Ex. No.	n	z	R_1	-A-B-	L	
2	B1	2	-(CH$_2$)$_2$-	H	-CH=CH-CH=CH-	H	(5)
22	B9a	1	-C(=O)CH$_2$-	H	-CH=CH-CH=CH-	CH$_3$	
22a	B9a	1	-C(=O)CH$_2$-	H	-CH=CH-CH=CH-	CH$_3$	(6)
23	B9b	1	-C(=O)CH$_2$-	H	-CH=CH-CH=CH-	H	
23a	B9b	1	-C(=O)CH$_2$-	H	-CH=CH-CH=CH-	H	(6)

Co. No.	Ex. No.	n	z	R_1	-A-B-	L	
25	B1	1	$-CH_2-$	H	-CH=CH-CH=CH-	H	
25a	B1	1	$-CH_2-$	H	-CH=CH-CH=CH-	H	(3)
26	B9c	1	$-CHOH-CH_2-$	H	-CH=CH-CH=CH-	H	
27	B9d	1	-CH=CH-	H	-CH=CH-CH=CH-	H	
27a	B9d	1	-CH=CH-	H	-CH=CH-CH=CH-	H	(3)
28	B1	1	$-(CH_2)_3-$	H	-CH=CH-CH=CH-	H	
33	B1	1	$-O-CH_2-$	H	-CH=CH-CH=CH-	H	
33a	B1	1	$-O-CH_2-$	H	-CH=CH-CH=CH-	H	(3)
36	B5	1	$-(CH_2)_3-$	H	-CH=CH-CH=CH-	$C(=O)OC(CH_3)_3$	
37	B2b	1	$-(CH_2)_3-$	CH_2OH	-CH=CH-CH=CH-	$C(=O)OC(CH_3)_3$	
38	B6e	1	$-(CH_2)_3-$	CH_2OH	-CH=CH-CH=CH-	H	
40	B5	1	$-(CH_2)_2-$	H	$-CH=C(OCH_3)-C(OCH_3)=CH-$	$C(=O)OC(CH_3)_3$	
42	B1	1	$-(CH_2)_4-$	H	-CH=CH-CH=CH-	H	
44	B8	1	$-(CH_2)_2-$	Cl	$-CH=C(OCH_3)-C(OCH_3)=CH-$	$C(=O)OC(CH_3)_3$	
44a	B6e	1	$-(CH_2)_2-$	Cl	$-CH=C(OCH_3)-C(OCH_3)=CH-$	$C(=O)OC(CH_3)_3$	(3)
45	B2b	1	$-(CH_2)_2-$	CH_2OH	$-CH=C(OCH_3)-C(OCH_3)=CH-$	$C(=O)OC(CH_3)_3$	
47	B1	1	$-CH_2-$	H	$-CH=C(OCH_3)-C(OCH_3)=CH-$	H	
47a	B1	1	$-CH_2-$	H	$-CH=C(OCH_3)-C(OCH_3)=CH-$	H	(3)
56	B2c	1	-CH=CH-	H	-CH=CH-S-	H	
56a	B2c	1	-CH=CH-	H	-CH=CH-S-	H	(3)

(3) (E)-2-butenedioate (1:1); (5) hydrochloric acid (1:1); (6) (E)-2-butenedioate (2:3)

Claims

1. A compound of formula



(I)

a prodrug, a *N*-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof wherein

R^1 is hydrogen, C_{1-6}alkyl, halo, formyl, carboxyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl, $N(R^3R^4)C(=O)$-, $N(R^3R^4)C(=O)N(R^5)$-, ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, $N(R^3R^4)C(=O)$-, C_{1-6}alkyl$C(=O)N(R^5)$-, C_{1-6}alkyl$S(=O)_2N(R^5)$- or $N(R^3R^4)C(=O)N(R^5)$-;

wherein each R^3 and each R^4 independently are hydrogen or C_{1-4}alkyl;

R^5 is hydrogen or hydroxy;

R^2 independently is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, $N(R^3R^4)C(=O)$-, aryl or halo;

n is 1 or 2;

-A-B- represents a bivalent radical of formula

-Y-CH=CH-	(a-1);
-CH=CH-Y-	(a-2); or
-CH=CH-CH=CH-	(a-3);

wherein each hydrogen atom in the radicals (a-1) to (a-3) may independently be replaced by R^6 wherein R^6 is selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, formyl, carboxyl and hydroxycarbonylC_{1-6}alkyl;

each Y independently is a bivalent radical of formula -O-, -S- or $-NR^7$-; wherein R^7 is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

Z is is a bivalent radical of formula

$-(CH_2)_p$-	(b-1),
-CH=CH-	(b-2),
$-CH_2$-CHOH-	(b-3),
$-CH_2$-O-	(b-4),

$-CH_2-C(=O)-$ (b-5), or

$-CH_2-C(=NOH)-$ (b-6),

provided that the bivalent radicals (b-3), (b-4), (b-5) and (b-6) are connected to the nitrogen of the imidazole ring via their $-CH_2-$ moiety;

wherein p is 1, 2, 3 or 4;

L is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl or C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, polyhaloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or polyhaloC_{1-4}alkyloxy;

provided that 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*],4'-piperidine] is not included.

2. A compound according to claim 1 wherein -A-B- is a bivalent radical of formula -CH=CH-CH=CH- (a-3).

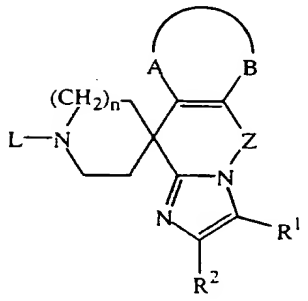
3. A compound according to claim 1 or 2 wherein Z is $-(CH_2)_p-$ (b-1), -CH=CH- (b-2), or $-CH_2-O-$ (b-4).

4. A compound according to any one of claims 1 to 3 wherein L is hydrogen, C_{1-6}alkyl, carboxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyloxycarbonylC_{1-6}alkyl.

5. A compound according to any one of claims 1 to 4 wherein R^1 is hydroxyC_{1-6}alkyl, formyl, C_{1-6}alkyloxycarbonyl, $N(R^3R^4)C(=O)-$, halo or hydrogen.

6. A compound according to claim 1 wherein the compound is 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide; 5,6-dihydrospiro[11*H*-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanol; 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11*H*],4'-piperidine]; and 1'-butyl-5,6-dihydrospiro[imidazo[2,1-b] [3] benzazepine-11-[11H],4'-piperidine], a prodrug, a *N*-oxide, an addition salt, or a quaternary amine thereof.

7. A compound of formula



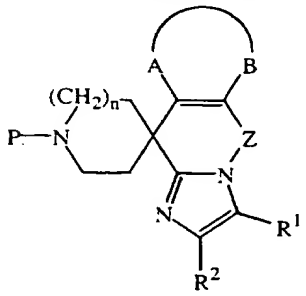
(I)

a prodrug, a *N*-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof wherein L, n, -A-B-, Z, R^1 and R^2 are defined as in claim1 for use as a medicine.

8. A pharmaceutical comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 7.

9. A process of preparing a composition as claimed in claim 8, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as described in any one claims 1 to 7.

10. A compound of formula

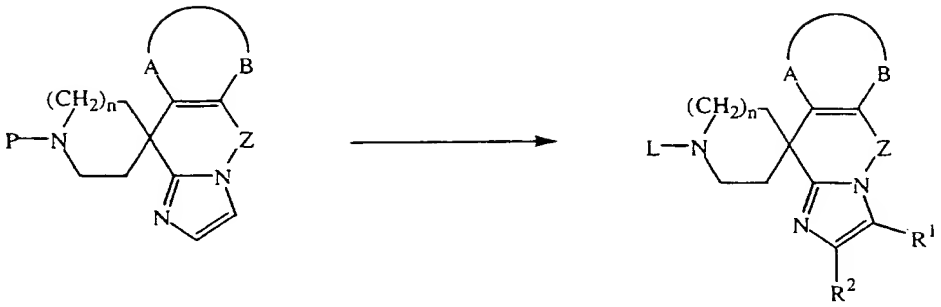


(II-a)

a *N*-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof wherein P is a protective group and n, -A-B-, Z, R^1 and R^2 are defined as in claim1.

11. A process of preparing a compound as claimed in claim 1, characterized by,

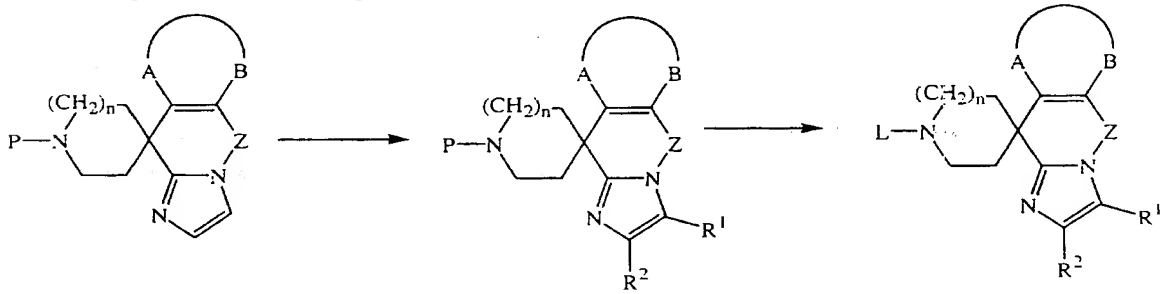
a) deprotecting an intermediate of formula (II), followed optionally by derivatizing either the piperidine moiety, or the imidazole moiety, or both the piperidine moiety and the imidazole moiety



(II) (I)

with -A-B-, Z, L, R^1 and R^2, and n defined as in claim 1 and P being a protective group;

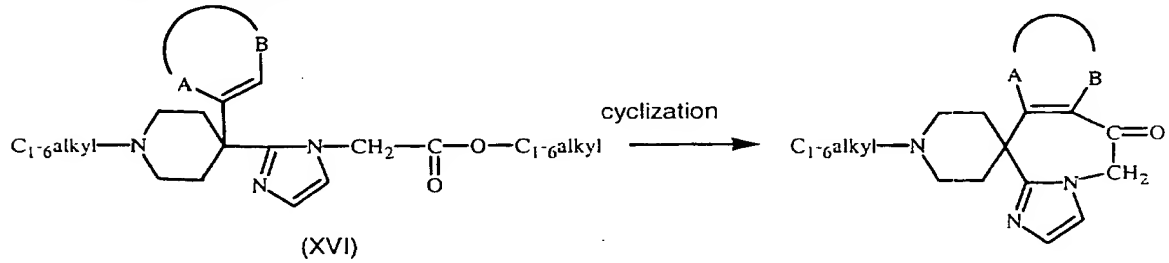
b) derivatizing an intermediate of formula (II) at the imidazole moiety, leading to the formation of an intermediate of formula (II-a), followed by deprotecting the piperidine moiety, and followed optionally by derivatizing the piperidine moiety



(II) (II-a) (I)

with -A-B-, Z, L, R^1 and R^2, and n defined as in claim 1 and P being a protective group;

c) by cyclizing an intermediate of formula (XVI) in the presence of an appropriate acid, leading to a compound of formula (I-m)



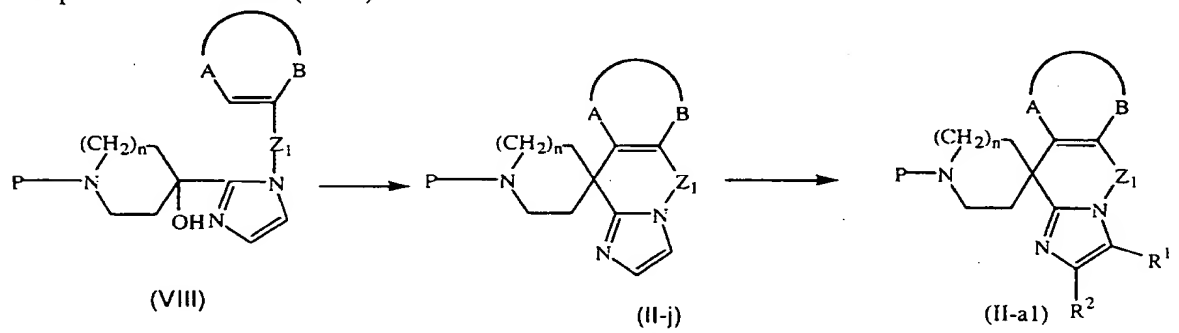
(XVI) (I-m)

with -A-B- defined as in claim 1;

and, if desired, converting compounds of formula (I) and (I-a) into each other following art-known transformations, and further, if desired, converting the compounds of formula

(I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

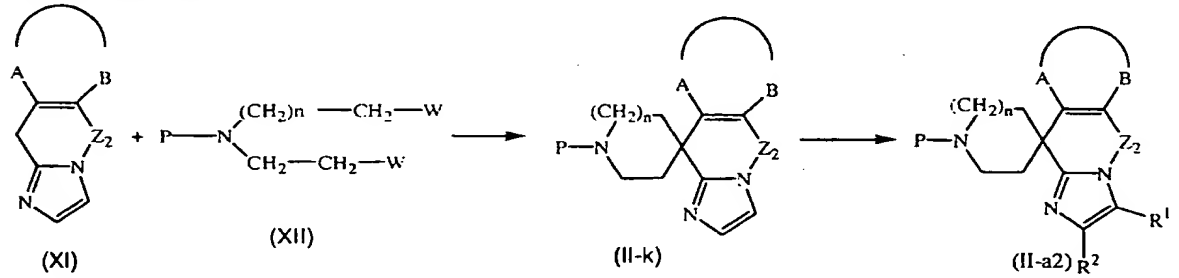
12. A process of preparing a compound as claimed in claim 10, characterized by,
a) cyclizing a compound of formula (VIII) with an appropriate acid, leading to a compound of formula (II-j), followed optionally by derivatizing the imidazole moiety, leading to a compound of formula (II-a1)



(VIII) (II-j) (II-a1)

with -A-B-, R^1, R^2 and n defined as in claim 1, P being a protective group and Z_1 being a bivalent radical of formula $-(CH_2)_p-$, wherein p is 1,2,3 or 4.

b) by reacting a tricyclic moiety of formula (XI) with a reagent of formula (XII) under an inert atmosphere in a reaction inert solvent in the presence of a suitable base,leading the a compound of formula (II-k), followed optionally by derivatizing the imidazole moiety leading to a compound of formula (II-a2)



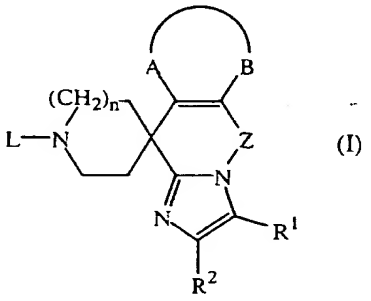
(XI) (XII) (II-k) (II-a2)

with -A-B-, R^1, R^2 and n defined as in claim 1, P being a protective group, W being a suitable leaving group, e.g. a halo, and Z_2 being a bivalent radical of formula $-(CH_2)_p-$, or $-CH_2-O-$, wherein p is 1,2,3 or 4.

ABSTRACT

ANTIHISTAMINIC SPIRO COMPOUNDS

This invention concerns the compounds of formula



(I)

a prodrug, a *N*-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof wherein R^1 is hydrogen, C_{1-6}alkyl, halo, formyl, carboxyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl, $N(R^3R^4)C(=O)$-, $N(R^3R^4)C(=O)N(R^5)$-, ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, $N(R^3R^4)C(=O)$-, C_{1-6}alkyl$C(=O)N(R^5)$-, C_{1-6}alkyl$S(=O)_2N(R^5)$- or $N(R^3R^4)C(=O)N(R^5)$- wherein each R^3 and each R^4 independently are hydrogen or C_{1-4}alkyl, and R^5 is hydrogen or hydroxy; R^2 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, $N(R^3R^4)C(=O)$-, aryl or halo; n is 1 or 2; -A-B- represents a bivalent radical of formula -Y-CH=CH-, -CH=CH-Y-, or -CH=CH-CH=CH-, wherein each hydrogen atom may independently be replaced by R^6 wherein R^6 is C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, ethenyl substituted with carboxyl or C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, formyl, carboxyl or hydroxycarbonylC_{1-6}alkyl, and each Y independently is a bivalent radical of formula -O-, -S- or $-NR^7$-, wherein R^7 is hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl; Z is is a bivalent radical of formula $-(CH_2)_p$-, -CH=CH-, $-CH_2$-CHOH-, $-CH_2$-O-, $-CH_2$-C(=O), or $-CH_2$-C(=NOH)-, provided that the bivalent radicals are connected to the nitrogen of the imidazole ring via their $-CH_2$- moiety; and wherein p is 1, 2, 3 or 4; L is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl or C_{1-6}alkyl substituted with hydroxy, carboxyl, C_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl; aryl is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, polyhaloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or polyhaloC_{1-4}alkyloxy; as antihistaminic agents; their preparation, compositions containing them and their use as a medicine.